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REVIEW

Role of tumour necrosis factor alpha converting enzyme (TACE/ADAM17) and associated proteins in coronary artery disease and cardiac events

Rôle de l'enzyme de conversion TNF (TACE/ADAM17) et des protéines associées dans la maladie coronaire et les événements cardiaques

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Summary Tumour necrosis factor alpha converting enzyme (TACE/ADAM17) is a member of the A disintegrin and metalloproteinase (ADAM) family of ectodomain shedding proteinases. It regulates many inflammatory processes by cleaving several transmembrane proteins, including tumour necrosis factor alpha (TNF α) and its receptors tumour necrosis factor alpha receptor 1 and tumour necrosis factor alpha receptor 2. There is evidence that TACE is involved in several

Abbreviations: ACS, Acute coronary syndrome; AMI, Acute myocardial infarction; CAD, Coronary artery disease; MACE, Major adverse cardiac events; MAPK, Mitogen-activated protein kinases; TACE (CD156b), Tumour necrosis factor alpha converting enzyme or A disintegrin and metalloproteinase 17 (ADAM17); TIMP3, Tissue inhibitor of metalloproteinase 3; TNF α , Tumour necrosis factor alpha; TNFR, TNF receptor.

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Biomarker;
TACE

inflammatory diseases, such as ischaemia, heart failure, arthritis, atherosclerosis, diabetes and cancer as well as neurological and immune diseases. This review summarizes the latest discoveries regarding the mechanism of action and regulation of TACE. It also focuses on the role of TACE in atherosclerosis and coronary artery disease (CAD), highlighting clinical studies that have investigated its expression and protein activity. The multitude of substrates cleaved by TACE make this enzyme an attractive target for therapy and a candidate for biomarker research and development in CAD.

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MOTS CLÉS

Athérosclérose ;
Protéines
transmembranaires ;
TNF α ;
Biomarqueur ;
TACE

Résumé L'enzyme de conversion du facteur alpha de nécrose tumorale (TACE/ADAM17), membre de la famille des A désintégrines et métalloprotéinases (ADAM) qui sont des protéinases clivant l'ectodomaine des protéines transmembranaires, régule différents processus inflammatoires en clivant des protéines transmembranaires, y compris le facteur alpha de nécrose tumorale (TNF α) et ses récepteurs 1 et 2. Différentes études ont montré l'association de TACE avec des maladies inflammatoires tel que l'ischémie, l'insuffisance cardiaque, l'arthrite, l'athérosclérose, le diabète, le cancer ainsi que des maladies neurologiques et immunologiques. Cette revue résume les dernières découvertes concernant le mécanisme d'action et de régulation de TACE ainsi que son rôle dans l'athérosclérose et les maladies coronariennes en mettant en évidence les études cliniques les plus récentes en relation avec son expression et son activité. La multitude des substrats clivés par TACE rendent cette enzyme une cible thérapeutique intéressante surtout dans le domaine du développement des biomarqueurs pour les maladies coronariennes.

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Background

Tumour necrosis factor alpha converting enzyme (TACE), also known as A disintegrin and metalloproteinase 17 (ADAM17), is a membrane-anchored protein responsible for the ectodomain shedding of a variety of transmembrane proteins, such as cytokines, chemokines, and growth factors and their receptors. Shedding results in the initiation or inhibition of downstream signalling and cellular responses, and is associated with several major acute and chronic inflammatory diseases. Recent studies have reported overexpression of TACE in patients with coronary artery disease (CAD) as well as after acute myocardial infarction (AMI), indicating that TACE may be a useful cardiac prognostic biomarker of cardiac events. This review summarizes recent findings on TACE activity and regulation, with an emphasis on the role of TACE in CAD.

Structure

Black et al. first described TACE in 1997 when working with mammalian THP1 cells, as the enzyme that cleaves tumour necrosis factor alpha (TNF α), and reported purification and cloning of the protein [1]. Subsequently, different forms of TACE have been described including the full-length protein (~110 kDa under non-reducing conditions), a mature form of TACE lacking the prodomain (80 kDa), and a third form

detected in cell lysates, which lacks the cytoplasmic domain (60 kDa) [2] (Fig. 1).

Localization

Immunohistochemical studies suggest that most of the active form of TACE is localized in the cellular perinuclear region, with a small amount present on the plasma membrane surface [2]. Tellier et al. further reported that TACE is sequestered into lipid rafts (Fig. 2). This spatial distribution has a role in the regulation of TACE activity by keeping the enzyme separate from its substrates [3].

Lipid rafts are known to have high concentrations of cholesterol, and interestingly, the shedding of TACE substrates, such as CD30 [4], interleukin-6 receptor (IL-6R) [5] and L-selectin (CD62L) [6], can be increased by cholesterol-lowering drugs. The increase in TACE shedding was also observed with TNF α , TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2) after membrane cholesterol depletion [3]. Disruption of the lipid rafts may displace the mature form of TACE in the non-raft region of the membrane that contains the major part of TACE substrates, and increase their shedding. Therefore, under normal conditions, the sequestration of the mature form of TACE in lipid rafts can be considered as the rate-limiting process of its shedding activity [7].

Activation and regulation

Tissue inhibitor of metalloproteinase 3 (TIMP3) is the only known endogenous inhibitor of TACE [8].

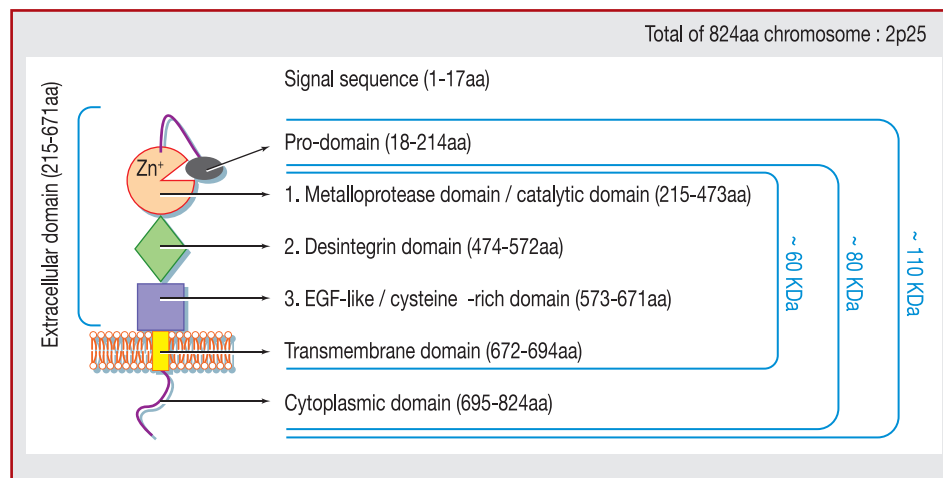


Figure 1. TACE domains. Signal peptide (1-17 aa); pro-domain (18-214 aa) acting as an inactivator and a chaperone domain; extracellular domain (215-671 aa) comprising: 1. A metalloprotease domain/catalytic domain (215-473 aa) responsible for an ectodomain shedding; 2. A disintegrin domain (474-572 aa); 3. An EGF-like/cysteine rich domain (573-671 aa) responsible for substrate recognition and activation; transmembrane domain (672-694 aa) necessary for effective cleavage of substrates; cytoplasmic domain (695-824 aa) binding to many proteins that regulate TACE activity. aa: amino acid; EGF: endothelial growth factor; TACE: tumour necrosis factor alpha converting enzyme.

TIMP3 is downregulated in circulating human monocytes in people at high risk of diabetes and atherosclerosis [9]. Stöhr et al. demonstrated that *TIMP3* also regulates lipid metabolism as well as the oxidative stress response, maintaining metabolic flexibility in the heart, particularly during episodes of increased cardiac stress [10]. *TIMP3* over expression has been shown to improve post-myocardial infarction cardiac remodelling related to lower extracellular matrix disruption in animal models [11,12].

Regarding *TIMP3* activation, Cesaro et al. showed that strong TACE expression was associated with early acute phase inflammation in Crohn's disease, whereas *TIMP3* was upregulated during the quiescent phase of the disease [13]. *TIMP3* may therefore be involved in a delayed regulatory mechanism following an increased TACE expression, and its role in inflammation and heart related diseases should be studied further.

Studies have shown that only the monomeric form of TACE is active and can effectively cleave its substrates. However, TACE appears to be predominantly present as dimers at the cell surface, which enables its efficient association with *TIMP3* and silences its activity. Hence, *TIMP3* inhibits TACE only when it is in its dimer form. Upon activation of the p38 mitogen-activated protein kinase pathway, the balance can shift from TACE dimers to monomers, and this shift is associated with an increase in cell surface presentation of TACE and a reduction in *TIMP3* association [14].

Substrates and shedding process

TACE mediates cell-cell interactions with a wide range of identified substrates, although the mechanisms and consequences of this binding are not yet fully understood. As the sequences cleaved in various substrates are highly variable, there is no apparent consensus for the TACE cleavage sequence. New evidence suggests that TACE activity is regulated by its non-catalytic domains and the secondary structure of its substrates [15].

Cleavage of TACE substrates occurs at extracellular sites proximal to the cell membrane, thereby releasing the soluble ectodomain from the cell surface. The cleaved molecules can then bind to their receptor on the same cell (autocrine effect) or to receptors on neighbouring cells (paracrine effect) or even enter the bloodstream (endocrine effect). When the substrate is cleaved and bound to its receptor, it can initiate downstream signalling events. Alternatively, the receptor can also be cleaved from the cell surface; thus, ectodomain shedding can actually stop the ligand-initiated signalling.

Because of its many functional properties, TACE plays a major role in inflammation through its shedding of a variety of inflammatory substrates. Studies have shown that TACE is implicated in platelet function through its cleavage of the von Willebrand factor (CD42b) receptor [16]. TACE is also responsible for the cleavage of L-selectin (CD62L), intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) [17]. Many TACE substrates have been extensively investigated in atherosclerosis, and all are known to participate in the inflammatory process accompanying the formation and progression of plaque (Fig. 3). The consequences of TACE shedding on these factors needs to be closely investigated, as their soluble forms may hold different properties compared to their membrane forms. For example, the cleavage of TNFR1 by TACE sheds a soluble form of TNFR1 that binds to free TNF α , dampening the inflammatory response [18]. In addition, TACE activates ligands (such as neuregulin) that bind to the ErbB tyrosine kinase family of receptors. The resulting signalling pathways have been involved in the growth of many tumour types as well as the maintenance of cardiac function [19,20].

The fate of TACE after its activation

There appears to be contradiction in the understanding what happens to TACE after it has been activated, and many postulations have been made.

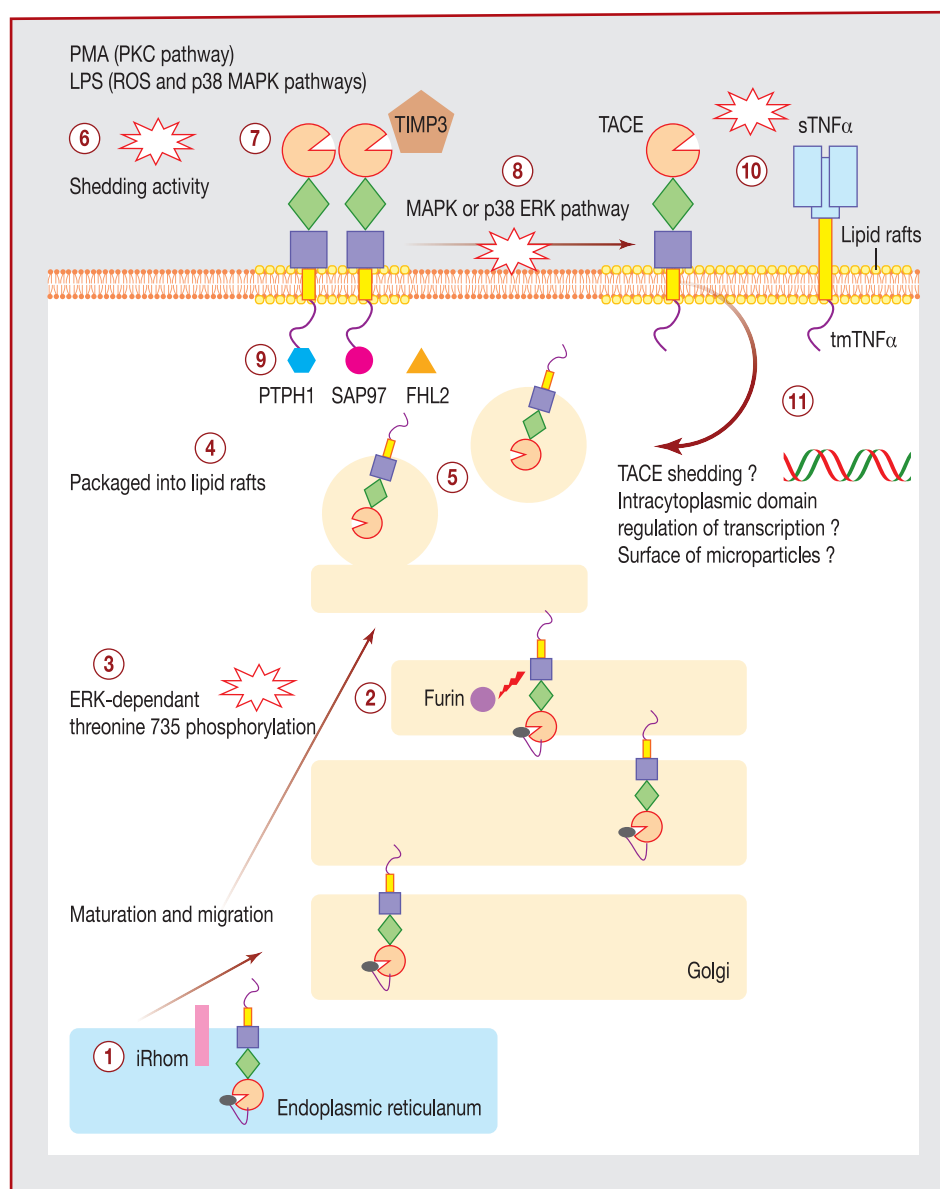


Figure 2. TACE activation and regulation. 1. Once synthesized, iRhomb bind to TACE and promotes maturation, its exit from the endoplasmic reticulum and its migration to the Golgi. 2. TACE prodomain is cleaved by furin in the trans-Golgi network. 3. During maturation, ERK-dependent threonine 735 phosphorylation is necessary for TACE to reach the secretory pathway. 4. TACE is packaged into lipid rafts during its transport and maturation through the Golgi. 5. Most of the active form of TACE is localized in the cellular perinuclear region, with a small amount present in the plasma membrane. 6. TACE has an increased shedding rate when exposed to cell activators, such as phorbol esters, including PMA. Other activators include lipopolysaccharide, which is dependent on ROS and the p38 MAPK pathway. 7. TACE is present in dimers on the cell surface and binds to its inhibitor TIMP3. 8. Activation of the ERK or p38 MAPK pathway transforms TACE from a dimer structure into a monomer structure and releases it from TIMP3. 9. TACE is regulated by FHL2 and SAP97. 10. TACE cleaves transmembrane TNF α and releases soluble TNF α . ER: endoplasmic reticulum; ERK: extracellular signal-regulated kinases; FHL2: four and a half LIM domains 2; LPS: lipopolysaccharide; iRhomb2: rhomboid family member 2; MAPK: mitogen-activated protein kinases; PKC: protein kinase C; PMA: phorbol myristate acetate; PTPH1: protein-tyrosine phosphatase; ROS: reactive oxygen species; SAP97: synapse-associated protein 97; sTNF α : soluble TNF α ; TACE: tumour necrosis factor alpha converting enzyme; TIMP3: tissue inhibitor of metalloproteinases 3; tmTNF α : transmembrane TNF α ; TNF α : tumour necrosis factor alpha.

ADAM10, another member of the ADAM family, is known to undergo regulated intramembrane proteolysis by presenilin after its ectodomain is shed by ADAM-9 or ADAM-15 [21]. In the intramembrane proteolysis process, a membrane protein typically undergoes two consecutive cleavages. The first results in the shedding of its ectodomain; the second one occurs within its transmembrane domain, resulting in

secretion of a small peptide and the release of the intracellular domain into the cytosol. After intramembrane proteolysis, the cytoplasmic domain of ADAM10 can translocate to the nucleus to bind to gene loci undergoing transcription. Since ADAM10 is the closest relative of TACE, there is a high possibility that the cytoplasmic domain of TACE itself can undergo intramembrane

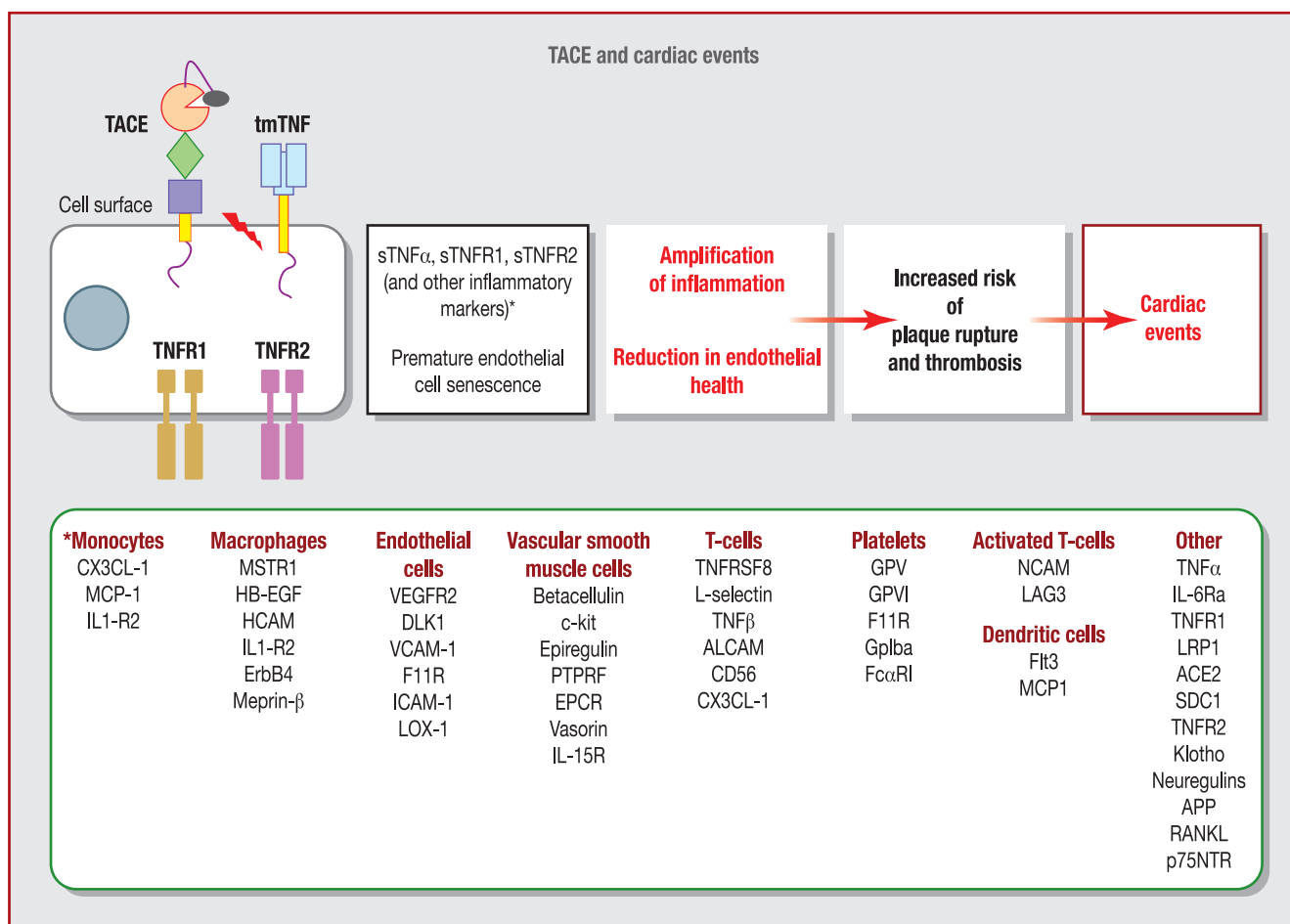


Figure 3. Possible role of TACE in cardiac events. This diagram shows the different proteins cleaved by TACE that are involved in chronic arterial wall inflammation occurring in atherosclerosis. As an example, TACE cleaves transmembrane TNFα, TNFR1 and TNFR2 releasing their soluble forms, sTNFα, sTNFR1 and sTNFR2, respectively. The transmembrane ectodomain shedding combined with a premature endothelial cell senescence due to TACE, leads to amplification of inflammation as well as reduction in endothelial health. This results in an increased risk of plaque rupture and thrombosis, and an overall increased risk of developing cardiovascular events. sTNFα: soluble tumour necrosis factor alpha; sTNFR1: soluble tumour necrosis factor alpha receptor 1; sTNFR2: soluble tumour necrosis factor alpha receptor 2; TACE: tumour necrosis factor alpha converting enzyme; tmTNFα: transmembrane TNFα; TNFα: tumour necrosis factor alpha; TNFR1: tumour necrosis factor alpha receptor 1; TNFR2: tumour necrosis factor alpha receptor 2.

proteolysis and participate in gene transcription regulation. A recent study reported that TACE can play a role in post-myocardial infarction recovery by regulating vascular endothelial growth factor receptor-2 transcription and angiogenesis in cardiomyocytes [22]. Whether TACE is internalized and downregulated after activation is still unclear. However, recent studies have reported that soluble TACE can be detected in the plasma [23,24], which is suggestive of a particular mechanism behind its own shedding, a process that remains unknown.

TACE and cardiovascular disease

TACE in heart diseases

Several studies have investigated the role of TACE in heart diseases. Investigators found that TACE expression was increased in endomyocardial tissues in myocarditis, as well as in the peripheral blood in advanced stages of

heart failure. TACE was upregulated together with TNFα in myocarditis and negatively correlated with left ventricular systolic function [25]. Patients with advanced congestive heart failure also had an increased expression of TACE and TNFα compared to controls [26]. The role of TACE has been highlighted in aortic aneurysm [27] and in heart development [28]. Interestingly, Takayanagi et al. recently reported that TACE may be a novel therapeutic target for the prevention of hypertensive complications [29].

TACE and CAD

The underlying pathological process behind the development and progression of CAD is atherosclerosis, which results from an imbalance in lipid metabolism and a maladaptive immune response leading to chronic inflammation in the arterial wall. Major adverse cardiac events (MACE) often occur suddenly in patients with CAD after a revascularization strategy, resulting in high mortality and morbidity. These events include death, stroke, myocardial infarction, heart

failure and repeat coronary revascularization of the target lesion [30]. Many studies are currently investigating the association between different cardiovascular markers and MACE with a recent interest in multiple marker models versus a single marker model [31]. However, the investigation of TACE and associated proteins as a multiple marker model for MACE prediction has not yet been evaluated.

Clinical studies of TACE and associated proteins in CAD and AMI

Several studies have demonstrated that TACE plays a role in CAD initiation and progression to an acute coronary syndrome (ACS). Clinical studies have shown elevated plasma levels of $\text{TNF}\alpha$ in patients with AMI, suggesting that $\text{TNF}\alpha$ maturation, which relies on TACE, may activate systemic inflammation and contribute to plaque rupture [32]. Subsequent studies have found a positive association between TACE in AMI, as summarized in Table 1. Increased levels of gene expression of $\text{TNF}\alpha$ and TACE were found in circulating leucocytes of patients with myocardial infarction, obtained within 24 hours of onset [33]. The Killip-Kamball classification system is used in patients with an ACS to stratify their risk of mortality regarding the development of heart failure. Expression of TACE and $\text{TNF}\alpha$ was significantly higher in patients with Killip-Kamball class III or IV AMI than in those with class I or II AMI or in controls [34]. This finding demonstrates that higher levels of TACE-associated inflammation correlate with an increased risk of developing severe heart failure after an ACS. Shimoda et al. [35] reported that TACE gene expression levels in peripheral blood cells were higher in patients with AMI compared to healthy subjects, and particularly in those who had complications, such as malignant recurrent ventricular arrhythmia or pump failure. Both spontaneous and phorbol 12-myristate 13-acetate (PMA)-stimulated levels of TACE gene expression as well as $\text{TNF}\alpha$ gene and protein expression levels were found to be higher in patients with AMI compared to healthy subjects. Sustained increases in TACE and $\text{TNF}\alpha$ levels were reported 14 days after the onset of AMI and levels correlated positively with peak creatinine kinase levels.

Systemic gene expression levels of TACE and $\text{TNF}\alpha$ were documented to be higher in patients with AMI compared to patients with stable angina [36]. Interestingly, TACE levels were higher in local samples, near areas of ruptured coronary plaques, than in systemic samples obtained from patients with AMI. TACE and $\text{TNF}\alpha$ immunostaining showed that they were localized in infiltrating macrophages in ruptured coronary plaque/thrombus materials occluding the culprit coronary artery. In addition, increased levels of TACE in culprit coronary samples were the strongest independent predictor of adverse cardiac events (6 months after the onset of AMI) after adjustment for various clinical variables. The authors suggested that local expression of TACE in the culprit coronary artery leads to arterial remodelling and rupture or erosion of weakened coronary plaque, leading to the exacerbation of cardiac events [36].

Rizza et al. [37] recently measured TACE activity by evaluating the levels of its main four substrates (soluble VCAM-1, soluble ICAM, soluble IL6R and soluble TNFR1) in subjects with established vascular atherosclerosis who were followed for secondary MACE. They identified three homo-

geneous subgroups of patients, in terms of event risk, and an increased risk for incident events was observed among individuals with a high TACE score. Looking closely at $\text{TNF}\alpha$ receptors, soluble TNFR2 levels were found to be increased in heart failure, and other studies have shown higher circulating levels of soluble TNFR1 and soluble TNFR2 associated with nephropathy, cardiovascular events, and total mortality in type 2 diabetes [38]. Canault et al. demonstrated that TACE-containing microparticles of atherosclerotic plaques are partly of endothelial origin and that TACE on the surface of microparticles was still active [39]. A more recent study showed TACE activity in the plasma of patients with anti-neutrophil cytoplasmic autoantibodies vasculitis and indicated that TACE was also present on plasma microparticles derived mainly from platelets but also from endothelial cells. The authors reported that it is the active form of TACE that is detectable in plasma samples and that it is found on the surface of microparticles originating from platelets as well as endothelial cells [24].

Other studies have investigated the role of TACE polymorphisms in relation to cardiovascular disease. In the Atherogene study, $\text{TNF}\alpha$, soluble TNFR1 , and soluble TNFR2 concentrations were all significantly elevated in patients with future cardiovascular death. Moreover, individuals carrying the 747Leu allele in TACE displayed a borderline increased risk of future cardiovascular death. This study also suggests a role of TACE in the regulation of $\text{TNF}\alpha$ plasma levels and identified the TACE gene as a candidate for CAD risk [40].

TACE activation in CAD

The association of TACE with CAD is due first, to its role in shedding a variety of inflammatory molecules (Fig. 3) and second, to some of its activators that have been shown to be associated with atherosclerosis and pathophysiological functions in CAD.

TACE has an increased shedding rate when exposed to cell activators, such as phorbol esters (e.g. PMA) [41], the p38 MAPK pathway and lipopolysaccharide, which is dependent on reactive oxygen species stimulation [42]. Oxidative stress generating reactive oxygen species is known to be involved in the progression of atherosclerosis, disturbed blood flow and arterial wall remodelling [43]. When reactive oxygen species are generated, TACE activation is increased as a result local and systemic inflammation. Moreover, it is known that nitric oxide can activate TACE [44]. Nitric oxide is involved in the physiological regulation of blood flow and has pathophysiological functions in CAD [44]. On the other hand, C-reactive protein is also known to activate TACE and the release of soluble lectin-like oxidized low-density lipoprotein receptor-1, which plays an important role in the development and progression of atherosclerosis [45]. Therefore, TACE is not one inflammatory factor among many, but is a key enzyme. Its activators and subsequently shed proteins are essential mediators in the development and progression of CAD (Fig. 3).

TACE, associated proteins and endothelial dysfunction in CAD

$\text{TNF}\alpha$ is a major contributor to inflammatory processes in CAD. On cleavage of transmembrane $\text{TNF}\alpha$ by TACE,

Table 1 Summary of studies of TACE and associated proteins, and their clinical implications in cardiovascular disease.

Model/disease	Site of TACE measurement	Methods	Animals	Results summary	Reference
<i>Heart disease: animal studies</i>					
Mouse (atherosclerosis)	Atherosclerotic lesions	IHC FC ELISA	Five-week-old apoE ^{-/-} male mice examined at 5, 10, 15 and 25 weeks of age (14 in each group) and wild-type mice (<i>n</i> =6) were fed a high-fat diet	Strong expression of TACE in atherosclerosis-prone sites (aortic sinus and arch) Plasma levels of sTNFR1 and sTNFR2 correlated with atherosclerotic severity	Canault et al., 2006 [63]
Timp3 ^{-/-} mouse	Heart tissue samples	qPCR WB	TIMP3-deficient mice (<i>n</i> =11) Age-matched wild-type littermates (<i>n</i> =9)	Loss of TIMP3 function triggered spontaneous left ventricular dilatation, cardiomyocyte hypertrophy, and contractile dysfunction at 21 months of age	Fedak et al., 2004 [33]
Rabbit	Sections from abdominal aorta Macrophages Tissues and cell lysate	IF qPCR WB	55 adult male New Zealand white rabbits and were then divided into 3 groups	TACE gene silencing reduced remodelling index and plaque burden and diminished the content of macrophages and lipids while increased that of smooth muscle cells and collagen in the aortic plaques The expression levels of TACE in unstable plaques were significantly higher than in stable plaques (42.6 ± 7.6 vs $25.2 \pm 6.5\%$, $P < 0.01$)	Zhao et al., 2015 [64]
<i>Heart disease: human studies</i>					
Atherosclerosis	Surface of microparticles	FC IHC	25 patients (symptomatic, <i>n</i> =10; asymptomatic, <i>n</i> =15) undergoing carotid endarterectomy 3 controls	Human plaque microparticles carried catalytically active TACE and significantly enhanced the cell surface processing of the TACE substrates TNF α , TNFR1 and endothelial protein C receptor	Canault et al., 2007 [39]
Myocarditis	Endomyocardial biopsy tissues	qPCR IHC	14 patients 5 controls	TNF α and TACE expression was significantly greater in the myocarditis group than in the control group ($P < 0.05$)	Satoh et al., 2000 [25]
CHF	PBMC	qPCR FC	46 patients 22 controls	TACE and TNF α gene expression, intracellular TACE and TNF α flow cytometry staining, and supernatant TNF α were higher in CHF patients than in controls ($P < 0.001$)	Satoh et al., 2004 [26]
AAA	Aortic sample	IHC	39 patients 8 controls	TACE gene expression was increased in human AAA samples compared with normal aorta	Kaneko et al., 2011 [27]

Table 1 (Continued)

Model/disease	Site of TACE measurement	Methods	Animals	Results summary	Reference
AMI within 24 h of onset	Circulating leukocytes	qPCR	37 patients 8 controls	TACE. TNF α gene expression was higher in circulating leucocytes in AMI patients compared with controls ($P < 0.01$)	Akatsu et al., 2003 [34]
AMI (blood samples on day 1 and day 14 after onset of myocardial infarction)	PBMC	qPCR FC	41 patients 15 controls	TACE and TNF α gene expression levels were higher in AMI patients than in healthy controls ($P < 0.001$) Levels of TACE and TNF α decreased 14 days after the onset of AMI The percentage of TACE and TNF α cells with positive staining was higher in AMI patients compared with healthy controls ($P < 0.001$)	Shimoda et al., 2005 [35]
AMI	Local samples from the plaque site Systemic samples from the aorta Thrombus material	qPCR FC IHC	60 AMI patients 21 stable angina patients	TACE and TNF α gene expression and protein levels in both local and systemic samples obtained from AMI patients were higher than those levels in systemic samples obtained from stable angina patients ($P < 0.001$) In AMI patients, these levels were higher in local samples than in systemic samples ($P < 0.001$) By the 6-month follow-up study, local TACE levels remained the only significant independent predictor of adverse cardiac events in AMI	Satoh et al., 2008 [36]
Acute stage of atherosclerotic ischaemic stroke	Platelet-rich plasma and platelet total protein samples	WB	306 patients 230 controls	Plasma TACE levels in the atherosclerotic ischaemic stroke group were higher than those in the control group ($P = 0.70$, $P = 0.000$)	Ling et al., 2013 [65]
Human atherosclerotic plaques	Surgical waste from endarterectomy pieces	IHC	4 human atherosclerotic plaques	TACE gene expression was observed in human atherosclerotic plaques	Canault et al., 2007 [39]
Cardiac surgery with cardiopulmonary bypass	Plasma sample at three time points: before anaesthesia, at the beginning of sternal wiring, 48 h after the first sample	ELISA	25 patients	Analysis of TACE activity did not show significant differences between the different time points ($P = 0.40$), but a trend of the medians was apparent towards higher values postoperatively and after 48 hours	Erdoes et al., 2013 [66]

Table 1 (Continued)

Model/disease	Site of TACE measurement	Methods	Animals	Results summary	Reference
<i>Other diseases: human studies</i>					
MCI and AD	Cerebrospinal fluid and human plasma	FRET WB	64 patients with AD, 88 subjects with MCI, and 50 age-matched healthy controls	Plasma TACE protein levels did not differ significantly in the three study groups. However, plasma TACE activity in subjects with MCI and AD patients was significantly higher than that in HC ($P < 0.001$) TACE enzymatic activity may increase progressively over the clinical course of AD	Sun et al., 2014 [23]
AAV	Plasma samples	ELISA FRET FC IHC	PR3-AAV active ($n = 47$) PR3-AAV remission ($n = 45$) Disease control ($n = 14$)	TACE protein levels were significantly increased in plasma samples from patients with active PR3-AAV compared with samples from patients in remission or from other controls with renal nonvascular diseases Plasma TACE retained its specific proteolytic activity and was partly located on extracellular microparticles Transcript levels of TACE were increased in blood samples of patients with active AAV	Bertram et al., 2015 [24]
Clinical malaria	Plasma samples	ELISA	Village infections ($n = 6$), uncomplicated malaria ($n = 39$), severe malaria ($n = 123$), non-malaria hospitalized ($n = 32$), Acute severe malaria/convalescent ($n = 19$)	Plasma levels of TACE were increased in Tanzanian children hospitalized with a malaria infection compared with asymptomatic children, but were similar to children hospitalized with other infectious diseases Plasma levels of TACE decreased during recovery after an acute malaria episode	Petersen et al., 2016 [67]
AAA: abdominal aortic aneurysm; AAV: active proteinase-3 (PR3)-positive ANCA-associated vasculitis; AD: Alzheimer's disease; AML: acute myocardial infarction; ANCA: antineutrophil cytoplasmic autoantibodies; CHF: congestive heart failure; ELISA: enzyme-linked immunosorbent assay; FC: flow cytometry; FRET: fluorescent resonance energy transfer; IF: immunofluorescence; IHC: immunohistochemistry assay; MIC: mild cognitive impairment; PBMC: peripheral blood mononuclear cells; qPCR: real time polymerase chain reaction; TIMP3: metalloproteinase inhibitor 3; TNF α : tumour necrosis factor alpha; TNFR1: TNF α receptor type 1; TNFR2: TNF α receptor type 2; sTNFR1: soluble TNFR1; sTNFR2: soluble TNFR2; WB: western blot.					

upregulation of TNF α can promote premature endothelial cell senescence and can participate in the ageing process of coronary arteries [46]. Recently, endogenous transmembrane TNF α was shown to protect against premature senescence in endothelial colony forming cells [47]. This is supported by a murine study in which transgenic mice that only express an uncleavable version of transmembrane TNF α developed fewer inflammatory atherosclerotic plaques than the wild-type mice [48].

It has been also reported that TNFR1 activates multiple signalling pathways that have been linked to apoptosis, endothelial cell dysfunction and inflammation, whereas TNFR2 signalling has been proven to be beneficial to the cardiovascular system by activating angiogenic and survival pathways [49]. Transmembrane TNF α has a higher affinity for TNFR2, which confers a survival signal, mediating angiogenic and blood vessel repair activities [50]. This suggests that transmembrane TNF α cleavage by TACE can have a deleterious effect on the protective and repair function properties provided by transmembrane TNF α . The role of TACE in vascular dysfunction was also highlighted in patients and mice, where ageing and obesity cooperatively reduced caveolin-1 expression and increased vascular endothelial TACE activity and soluble TNF α release in adipose tissue. This was believed to contribute to the development of remote coronary microvascular dysfunction in older obese patients [46].

TACE inhibition

As TACE seems to be implicated in many physiological processes, it is important to consider its inhibition and the potential consequences. Interestingly, a patient with homozygous TACE deficiency was identified [52] who, despite repeated skin infections and episodes of bowel disease, led a relatively normal life, indicating that loss of TACE in humans might have less severe consequences than in rodents [53]. The most promising TACE inhibition (without any major physiological consequences) seems to lie in the inhibition of its regulators. iRhom1 and 2 are needed for TACE transport to the cell surface (Fig. 2) and it is well established that iRhom2 is predominantly expressed in immune cells, such as neutrophils and macrophages [54], whereas iRhom1 is mostly expressed on non-immune cells [55]. Therefore, it is tempting to speculate that inhibition of iRhom2 would lead to a selective deficiency of TACE in neutrophils and macrophages with no effects on keratinocytes or intestinal epithelial cells where, in these cell types, iRhom1 would compensate for the blockade of iRhom2. Recently, it was found that reducing the release of TNF α in cardiomyocytes by pharmacologically attenuating the phosphorylation of TACE, reduced TNF α shedding activity by TACE [56]. It was also proven possible to inhibit specifically TACE activity by using its natural inhibitory domain and consequently modulating TNF α secretion in cells [57]. Another strategy of inhibiting TACE could be an injection of its inhibitor TIMP3 in the heart, which has been shown to prevent heart failure post-myocardial infarction [58]. However, since TACE inhibition will reduce TNF α activity, it is important to consider the complex cardiac effects observed after TNF α inhibition as it is becoming increasingly clear that a

minimum level of TNF α is important for the normal function of the heart [59,60].

Future work and conclusions

TACE plays a major role in controlling inflammatory processes and is involved in several chronic diseases. The number of known TACE substrates continues to increase, with mounting evidence that TACE is implicated in many cellular functions. Recent research indicates a particular role for TACE and the TNF family members in CAD and cardiovascular events, but none have really looked at this panel from a biomarker development point of view. Further investigations are, however, required to ascertain the exact role and mechanism of action of TACE in this disease area.

Future prospective studies in clinical cohorts at varying degrees of cardiovascular risk stratification are needed to fully assess TACE as a potential biomarker for CAD and MACE risk. This will be crucial for the future development of new personalized predictive tests and therapeutics that can improve patient clinical care pathways and prevent the high mortality rates associated with CAD.

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Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Black RA, Rauch CT, Kozlosky CJ, et al. A metalloproteinase disintegrin that releases tumour-necrosis factor- α from cells. *Nature* 1997;385:729–33.
- [2] Schlöndorff J, Becherer JD, Blobel CP. Intracellular maturation and localization of the tumour necrosis factor α convertase (TACE). *Biochem J* 2000;347(Pt 1):131–8.
- [3] Tellier E, Canault M, Rebsomen L, et al. The shedding activity of ADAM17 is sequestered in lipid rafts. *Exp Cell Res* 2006;312:3969–80.

- [4] von Tresckow B, Kallen KJ, von Strandmann EP, et al. Depletion of cellular cholesterol and lipid rafts increases shedding of CD30. *J. Immunol* 2004;172:4324–31.
- [5] Matthews V, Schuster B, Schütze S, et al. Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE). *J Biol Chem* 2003;278:38829–39.
- [6] Walev I, Tappe D, Gulbins E, Bhakdi S. Streptolysin O-permeabilized granulocytes shed L-selectin concomitantly with ceramide generation via neutral sphingomyelinase. *J Leukoc Biol* 2000;68:865–72.
- [7] Tellier E, Canault M, Poggi M, et al. HDLs activate ADAM17-dependent shedding. *J Cell Physiol* 2008;214:687–93.
- [8] Black RA. TIMP3 checks inflammation. *Nat Genet* 2004;36:934–5.
- [9] Cardellini M, Menghini R, Luzi A, et al. Decreased IRS2 and TIMP3 expression in monocytes from offspring of type 2 diabetic patients is correlated with insulin resistance and increased intima-media thickness. *Diabetes* 2011;60:3265–70.
- [10] Stöhr R, Kappel BA, Carnevale D, et al. TIMP3 interplays with apelin to regulate cardiovascular metabolism in hypercholesterolemic mice. *Mol Metab* 2015;4:741–52.
- [11] Angoulvant D, Fazel S, Weisel RD, et al. Cell-based gene therapy modifies matrix remodeling after a myocardial infarction in tissue inhibitor of matrix metalloproteinase-3-deficient mice. *J Thorac Cardiovasc Surg* 2009;137:471–80.
- [12] Tian H, Cimini M, Fedak PW, et al. TIMP-3 deficiency accelerates cardiac remodeling after myocardial infarction. *J Mol Cell Cardiol* 2007;43:733–43.
- [13] Cesaro A, Abakar-Mahamat A, Brest P, et al. Differential expression and regulation of ADAM17 and TIMP3 in acute inflamed intestinal epithelia. *Am J Physiol Gastrointest Liver Physiol* 2009;296:G1332–43.
- [14] Zheng Y, Schlondorff J, Blobel CP. Evidence for regulation of the tumor necrosis factor alpha-convertase (TACE) by protein-tyrosine phosphatase PTPH1. *J Biol Chem* 2002;277:42463–70.
- [15] Stawikowska R, Cudic M, Giulianotti M, Houghten RA, Fields GB, Minond D. Activity of ADAM17 (a disintegrin and metalloprotease 17) is regulated by its noncatalytic domains and secondary structure of its substrates. *J Biol Chem* 2013;288:22871–9.
- [16] Bergmeier W, Piffath CL, Cheng G, et al. Tumor necrosis factor-alpha-converting enzyme (ADAM17) mediates GPIIb/IIIa shedding from platelets in vitro and in vivo. *Circ Res* 2004;95:677–83.
- [17] Arribas J, Esselens C. ADAM17 as a therapeutic target in multiple diseases. *Curr Pharm Des* 2009;15:2319–35.
- [18] D'Alessio A, Esposito B, Giampietri C, Ziparo E, Pober JS, Filippini A. Plasma membrane microdomains regulate TACE-dependent TNFR1 shedding in human endothelial cells. *J Cell Mol Med* 2012;16:627–36.
- [19] Odiete O, Hill MF, Sawyer DB. Neuregulin in cardiovascular development and disease. *Circ Res* 2012;111:1376–85.
- [20] Wadugu B, Kühn B. The role of neuregulin/ErbB2/ErbB4 signaling in the heart with special focus on effects on cardiomyocyte proliferation. *Am J Physiol Heart Circ Physiol* 2012;302:H2139–47.
- [21] Tousseyn T, Thathiah A, Jorissen E, et al. ADAM10, the rate-limiting protease of regulated intramembrane proteolysis of Notch and other proteins, is processed by ADAMS-9, ADAMS-15, and the gamma-secretase. *J Biol Chem* 2009;284:11738–47.
- [22] Fan D, Takawale A, Shen M, et al. Cardiomyocyte A disintegrin and metalloproteinase 17 (ADAM17) is essential in post-myocardial infarction repair by regulating angiogenesis. *Circ Heart Fail* 2015;8:970–9.
- [23] Sun Q, Hampel H, Blennow K, et al. Increased plasma TACE activity in subjects with mild cognitive impairment and patients with Alzheimer's disease. *J Alzheimers Dis* 2014;41:877–86.
- [24] Bertram A, Lovric S, Engel A, et al. Circulating ADAM17 level reflects disease activity in proteinase-3 ANCA-associated vasculitis. *J Am Soc Nephrol* 2015;26:2860–70.
- [25] Satoh M, Nakamura M, Satoh H, Saitoh H, Segawa I, Hiramori K. Expression of tumor necrosis factor-alpha – converting enzyme and tumor necrosis factor-alpha in human myocarditis. *J Am Coll Cardiol* 2000;36:1288–94.
- [26] Satoh M, Iwasaka J, Nakamura M, Akatsu T, Shimoda Y, Hiramori K. Increased expression of tumor necrosis factor-alpha converting enzyme and tumor necrosis factor-alpha in peripheral blood mononuclear cells in patients with advanced congestive heart failure. *Eur J Heart Fail* 2004;6:869–75.
- [27] Kaneko H, Anzai T, Horiuchi K, et al. Tumor necrosis factor- α converting enzyme is a key mediator of abdominal aortic aneurysm development. *Atherosclerosis* 2011;218:470–8.
- [28] Shi W, Chen H, Sun J, et al. TACE is required for fetal murine cardiac development and modelling. *Dev Biol* 2003;261:371–80.
- [29] Takayanagi T, Forrester SJ, Kawai T, et al. Vascular ADAM17 as a novel therapeutic target in mediating cardiovascular hypertrophy and perivascular fibrosis induced by angiotensin II novelty and significance. *Hypertension* 2016;68:949–55.
- [30] Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. *J Am Coll Cardiol* 2008;51:701–7.
- [31] Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;355:2631–9.
- [32] Latini R, Bianchi M, Correale E, et al. Cytokines in acute myocardial infarction: selective increase in circulating tumor necrosis factor, its soluble receptor, and interleukin-1 receptor antagonist. *J Cardiovasc Pharmacol* 1994;23:1–6.
- [33] Fedak PW, Smookler DS, Kassiri Z, et al. TIMP-3 deficiency leads to dilated cardiomyopathy. *Circulation* 2004;110:2401–9.
- [34] Akatsu T, Nakamura M, Satoh M, Hiramori K. Increased mRNA expression of tumour necrosis factor-alpha and its converting enzyme in circulating leucocytes of patients with acute myocardial infarction. *Clin Sci Lond* 2003;105:39–44.
- [35] Shimoda Y, Satoh M, Nakamura M, Akatsu T, Hiramori K. Activated tumour necrosis factor-alpha shedding process is associated with in-hospital complication in patients with acute myocardial infarction. *Clin Sci Lond* 2005;108:339–47.
- [36] Satoh M, Ishikawa Y, Itoh T, Minami Y, Takahashi Y, Nakamura M. The expression of TNF-alpha converting enzyme at the site of ruptured plaques in patients with acute myocardial infarction. *Eur J Clin Invest* 2008;38:97–105.
- [37] Rizza S, Copetti M, Cardellini M, et al. A score including ADAM17 substrates correlates to recurring cardiovascular event in subjects with atherosclerosis. *Atherosclerosis* 2015;239:459–64.
- [38] Carlsson AC, Östgren CJ, Nystrom FH, et al. Association of soluble tumor necrosis factor receptors 1 and 2 with nephropathy, cardiovascular events, and total mortality in type 2 diabetes. *Cardiovasc Diabetol* 2016;15:40.
- [39] Canault M, Leroyer AS, Peiretti F, et al. Microparticles of human atherosclerotic plaques enhance the shedding of the tumor necrosis factor-alpha converting enzyme/ADAM17 substrates, tumor necrosis factor and tumor necrosis factor receptor-1. *Am J Pathol* 2007;171:1713–23.
- [40] Morange PE, Tregouet DA, Godefroy T, et al. Polymorphisms of the tumor necrosis factor-alpha (TNF) and the TNF-alpha converting enzyme (TACE/ADAM17) genes in relation to cardiovascular mortality: the AtheroGene study. *J Mol Med (Berl)* 2008;86:1153–61.
- [41] Hooper NM, Karran EH, Turner AJ. Membrane protein secretases. *Biochem J* 1997;321(Pt 2):265–79.

- [42] Scott AJ, O'Dea KP, O'Callaghan D, et al. Reactive oxygen species and p38 mitogen-activated protein kinase mediate tumor necrosis factor α -converting enzyme (TACE/ADAM-17) activation in primary human monocytes. *J Biol Chem* 2011;286:35466–76.
- [43] He F, Zuo L. Redox roles of reactive oxygen species in cardiovascular diseases. *Int J Mol Sci* 2015;16:27770–80.
- [44] Zhang Z, Kolls JK, Oliver P, et al. Activation of tumor necrosis factor- α -converting enzyme-mediated ectodomain shedding by nitric oxide. *J Biol Chem* 2000;275:15839–44.
- [45] Zhao XQ, Zhang MW, Wang F, et al. CRP enhances soluble LOX-1 release from macrophages by activating TNF- α converting enzyme. *J Lipid Res* 2011;52:923–33.
- [46] Csizsar A, Ungvari Z, Koller A, Edwards JG, Kaley G. Proinflammatory phenotype of coronary arteries promotes endothelial apoptosis in aging. *Physiol Genomics* 2004;17:21–30.
- [47] Green LA, Njoku V, Mund J, et al. Endogenous transmembrane TNF-alpha protects against premature senescence in endothelial colony forming cells. *Circ Res* 2016;118:1512–24.
- [48] Canault M, Peiretti F, Mueller C, et al. Exclusive expression of transmembrane TNF-alpha in mice reduces the inflammatory response in early lipid lesions of aortic sinus. *Atherosclerosis* 2004;172:211–8.
- [49] Luo D, Luo Y, He Y, et al. Differential functions of tumor necrosis factor receptor 1 and 2 signaling in ischemia-mediated arteriogenesis and angiogenesis. *Am J Pathol* 2006;169:1886–98.
- [50] Grell M, Becke FM, Wajant H, Männel DN, Scheurich P. TNF receptor type 2 mediates thymocyte proliferation independently of TNF receptor type 1. *Eur J Immunol* 1998;28:257–63.
- [52] Blaydon DC, Biancheri P, Di WL, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. *N Engl J Med* 2011;365:1502–8.
- [53] Peschon JJ, Slack JL, Reddy P, et al. An essential role for ectodomain shedding in mammalian development. *Science* 1998;282:1281–4.
- [54] Adrain C, Zettl M, Christova Y, Taylor N, Freeman M. Tumor necrosis factor signaling requires iRhom2 to promote trafficking and activation of TACE. *Science* 2012;335(6065):225–8.
- [55] Issuree PD, Maretzky T, McIlwain DR, et al. iRHO2 is a critical pathogenic mediator of inflammatory arthritis. *J Clin Invest* 2013;123:928–32.
- [56] Niu A, Wang B, Li Y-P. TNF α shedding in mechanically stressed cardiomyocytes is mediated by Src activation of TACE. *J Cell Biochem* 2015;116:559–65.
- [57] Wong E, Cohen T, Romi E, et al. Harnessing the natural inhibitory domain to control TNF α converting enzyme (TACE) activity in vivo. *Sci Rep* 2016;6:35598.
- [58] Martz L. Taking TIMP3 to heart. *SciBX* 2014;7:246.
- [59] Cacciapaglia F, Menna P, Navarini L, Afeltra A, Salvatorelli E, Minotti G. Matters of the heart: the case of TNF alpha-targeting drugs. *Mol Interv* 2011;11:79–87.
- [60] Balakumar P, Singh M. Anti-tumour necrosis factor-alpha therapy in heart failure: future directions. *Basic Clin Pharmacol Toxicol* 2006;99:391–7.
- [63] Canault M, Peiretti F, Kopp F, et al. The TNF alpha converting enzyme (TACE/ADAM17) is expressed in the atherosclerotic lesions of apolipoprotein E-deficient mice: possible contribution to elevated plasma levels of soluble TNF alpha receptors. *Atherosclerosis* 2006;187:82–91.
- [64] Zhao X, Kong J, Zhao Y, et al. Gene silencing of TACE enhances plaque stability and improves vascular remodeling in a rabbit model of atherosclerosis. *Sci Rep* 2015;5:17939.
- [65] Ling JY, Shen L, Liu Q, et al. Changes in platelet GPIb α and ADAM17 during the acute stage of atherosclerotic ischemic stroke among Chinese. *J Huazhong Univ Sci Technol Med Sci* 2013;33:438–42.
- [66] Erdoes G, Balmer ML, Slack E, et al. CD62L (L-Selectin) shedding for assessment of perioperative immune sensitivity in patients undergoing cardiac surgery with cardiopulmonary bypass. *Plos One* 2013;8:e53045.
- [67] Petersen JE, Mkumbaye SI, Vaaben AV, et al. Plasma Ang2 and ADAM17 levels are elevated during clinical malaria; Ang2 level correlates with severity and expression of EPCR-binding PfEMP1. *Sci Rep* 2016;6:35950.